Cell Penetrating Peptide Inhibiting the Main Protease of SARS-CoV-2

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As of October 2021, SARS-CoV-2 has infected over 244 million people and killed about 5 million people. The current FDA approved vaccines are effective; however, they lose their effectiveness after a few months of receiving both doses of the vaccine, and it is recommended to get a booster shot six months after receiving the second dose of the vaccine. Therefore, new highly effective, long lasting antiviral agents and strategies are needed to create an alternative treatment for SARS-CoV-2 and the different variants. Previous studies have shown that cell penetrating peptides (CPPs) have led to greater efficiency of intracellular delivery. However, no study is reported whether these peptides can be used to inhibit the viral proteins of SARS-CoV-2. The focus of this study is to identify cell penetrating antimicrobial peptides that have the most desirable binding affinities and interactions against the main protease of SARS-CoV-2. To identify these affinities and interaction, computational methods were employed. Peptides' structures were modelled by PEP-FOLD. Molecular docking and refinement were respectively performed by PATCH-DOCK, and FIRE-DOCK. Peptides with the highest levels of binding affinities and interactions with the active site residues of HIS41 and CYS145 were selected as the best candidates. Of the peptides being tested, R6/W3, gH625, GALA, and TP10 have shown the highest binding affinities against the main protease ranging from -45.58 to -55.58 kcal/mol. These peptides will be synthesized, and *in-vitro* experiments will be performed by FRET based 3CL-protease assay.